

# Urge Incontinence: Updates in Non-pharmacologic Treatments

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## Abstract

**Purpose of review** The aim of this manuscript is to provide an overview of the recent literature on non-pharmacologic therapies for urgency urinary incontinence (UUI), specifically focusing on treatments for adult women who suffer from UUI in the setting of idiopathic overactive bladder syndrome (OAB). **Recent findings** This review describes recent studies examining the efficacy of biofeedback-assisted pelvic muscle therapy, the effect of bariatric surgery on urinary incontinence, alternative approaches for tibial and transcutaneous nerve stimulation, sacral neuromodulation as compared to botulinum toxin type A, and 5-year outcomes of sacral neuromodulation therapy. The evidence supporting acupuncture as an alternative treatment is examined, and experimental therapies including electromagnetic nerve stimulation and fractional vaginal CO<sub>2</sub> laser therapy are reviewed. Emerging areas for UUI research including the urinary microbiome, urinary biomarkers, and considerations in refining future treatment guidelines are discussed.

**Summary** UUI is a complex disorder that can be improved by a wide variety of therapies. Non-pharmacologic therapies are effective and widely utilized treatment options for those suffering from UUI. As we continue to learn more about this burdensome condition, less invasive and more effective therapies will hopefully become more easily available with lower cost of care.

**Keywords** Urge incontinence · Overactive bladder · Neuromodulation · Non-pharmacologic therapy · Behavioral therapy

## Introduction

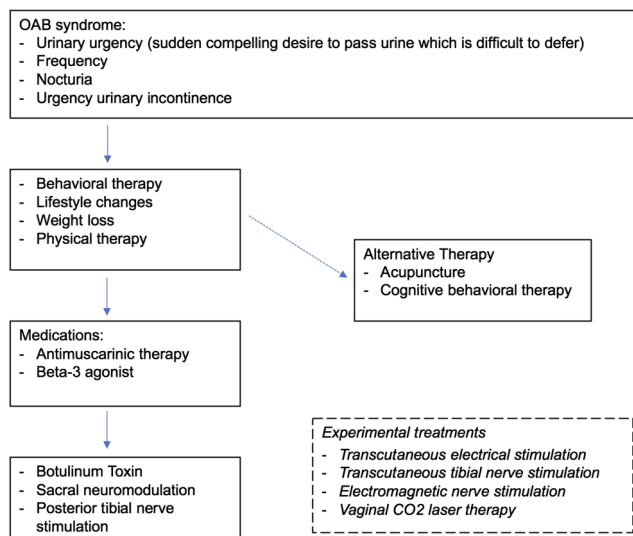
The last decade has been a time of significant advancement in the treatment of overactive bladder syndrome (OAB) and urgency urinary incontinence (UUI). The FDA approval for and subsequent widespread utilization of beta-3 agonist medication (mirabegron), botulinum toxin type A (BoNT/A), and neuromodulation (posterior tibial nerve stimulation and sacral neuromodulation) has given those suffering from OAB/UUI greater treatment choice, efficacy, and, as a result, satisfaction. The adoption of these therapies is an important step in advancing OAB therapy and heralds the development of innovative and mechanistically diverse treatments for this bothersome and prevalent condition.

Current AUA and ACOG guidelines for OAB treatment recommend initial first-line interventions of behavioral and lifestyle modifications, weight loss, and pelvic physical therapy with possible concomitant medication. For those patients who fail conservative management and who are unable to tolerate or do not respond to antimuscarinic or beta-3 agonist medication, next-line treatment options include neuromodulation and BoNT/A (Fig. 1) [1, 2]. Within this treatment paradigm, non-pharmacologic therapies offer effective treatment options and are a valuable alternative to pharmacologic therapy. A comprehensive systematic review of non-antimuscarinic therapy for OAB was recently conducted by Olivera and colleagues for the Society for Gynecologic Surgeons Systematic Review Group and was published in 2016 [3••]. Their review includes data from studies published through April 2014. This article will provide an overview of the more recent literature on non-pharmacologic therapies for OAB/

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**Fig. 1** Treatment overview

UUI, focusing specifically on clinically significant studies examining non-pharmacologic treatments for adult women with idiopathic OAB/UUI published within the past few years.

## Defining OAB/UUI

OAB is characterized by urinary urgency (a sudden compelling desire to pass urine which is difficult to defer), usually accompanied by frequency and nocturia with or without UUI, in the absence of urinary tract infection or other obvious pathology [4]. OAB affects an estimated 16% of the adult population impairing quality of life, burdening caregivers, and carrying substantial economic cost [5–9]. OAB is more common in women and the prevalence increases with older age. By 2050, there is expected to be a dramatic increase in the population suffering from OAB as the number of women over the age of 65 will more than double to nearly 50 million [9].

## Initial Management

Initial management of OAB/UUI involves conservative non-pharmacologic interventions (behavioral and lifestyle modifications, physical therapy) with recent treatment guidelines adding the option for concomitant pharmacologic therapy as an initial therapeutic option [1, 2]. The recent inclusion of pharmacologic therapy along with conservative first-line treatments likely results from the fact that conservative first-line interventions are not as well studied and many patients desire medical therapy at initial presentation. This should not overshadow that conservative non-pharmacologic initial interventions alone can provide significant improvement in UUI symptoms.

## Behavioral Modifications and Physical Therapy

For patients with less frequent leakage and those who wish to avoid more invasive therapies, first-line conservative treatments of behavioral and lifestyle modifications (bladder training, urge control techniques, pelvic floor muscle strengthening, fluid management, avoidance of bladder irritants, etc.), weight loss, and pelvic floor physical therapy can result in significant improvement in bothersome leakage and urgency symptoms. In their systematic review, Olivera and colleagues concluded that there is moderate evidence to show that weight loss, reduced caffeine and fluid intake, and pelvic floor muscle exercises significantly improve OAB/UUI symptoms [3•]. With increasing pressure on the medical field to develop quality of care indicators and to lower costs of care, it is probable that physicians will be assessed on whether they discuss and educate patients about these initial management options when treating patients with OAB/UUI.

A recent randomized controlled trial conducted by Voorham and colleagues investigated the efficacy of 9-weeks of biofeedback-assisted pelvic muscle therapy (BAPFMT) with a physical therapist as compared to instructions on toilet behavior and lifestyle modifications (bladder training, bladder diet, and fluid management). A total of 58 women were included in the study with 6 lost to follow-up (5 in BAPFMT arm and 1 in control arm). As compared to instructional handouts, BAPFMT was found to have a larger improvement in OAB complaints (as assessed by the Pelvic Floor Inventories), quality of life (assessed by the Kings Health Questionnaire), and significantly reduced urgency, leakage, and daily pad use on 24-h voiding diary and pad weight assessment [10•]. Interpretation of these results and the clinical relevance of these findings is limited by the lack of reporting the actual differences in numerical values for the reductions in urgency episodes, leakage episodes, and pad use. Additionally, the authors did not provide a definition for OAB used for their inclusion criteria so the exact study population is not clear—the manuscript did mention that seven of the patients were dry at baseline so it appears they included patients with OAB, with and without UUI. Regardless of the limitations of this specific study, it is logical (and has proven true in my own practice) that patients who are motivated and able to pursue pelvic floor physical therapy do better under the guidance of a properly trained pelvic floor physical therapist as compared to learning from educational handouts on their own.

We do know that weight loss improves urinary incontinence in addition to providing improved overall health for the patient. Over the past several years, multiple studies have been conducted to examine the effect of bariatric surgery on urinary incontinence. In 2017, a meta-analysis of 11 cohort studies evaluating the effects of bariatric surgery on pelvic floor disorders in obese women confirmed that bariatric surgery is associated with a significant improvement in urinary incontinence, as well as pelvic organ prolapse symptoms [11].

Further investigation into the mechanisms behind this association is needed to understand the relationship between obesity, and urinary urgency, frequency, and incontinence. We also need longer term follow-up studies to assess whether this initial improvement endures over time and how it correlates with maintaining a lower body weight over the long term.

## Nerve Stimulation

Posterior tibial nerve stimulation (PTNS) is widely utilized as an important therapy for refractory OAB in patients who want to avoid more invasive treatment or who have contraindications to sacral neuromodulation or BoNT/A. One of the main limitations of PTNS therapy is the significant burden on the patient as it requires regular visits to the physician's office for treatments (once a week for 12 weeks and then monthly thereafter as needed for booster sessions). A newer alternative for PTNS is currently under investigation. This new device is an implantable system that enables patients to perform stimulation sessions at home on a more regular basis after undergoing an implantation procedure. Preliminary results from a small study of 15 patients have shown that participants experienced a significant improvement in frequency, UUI, and quality of life over 3 months of use with low rates of adverse events [12•].

Another non-invasive treatment using surface electrodes that can be self-administered in one's own home is transcutaneous tibial nerve stimulation (TTNS). A recent systematic review by Booth et al. examined the effectiveness of TTNS for treatment of OAB [13•]. Thirteen papers (10 randomized trials and 3 prospective cohort studies) were included for a total of 629 participants, the vast majority being women. The authors concluded that TTNS is an effective, safe and well tolerated non-invasive therapy in women with idiopathic OAB. TTNS resulted in improvements in UUI, urgency, and frequency that were comparable to antimuscarinic treatment with TTNS being more acceptable to patients. However, the authors caution the interpretation of their results as studies were limited by small numbers and the risk of bias was unclear or high for the majority of randomized trials included in the review.

Additional approaches to transcutaneous electrical nerve stimulation (TENS) are also being investigated. Sharma et al. recently published results from a prospective study conducted in India examining transcutaneous nerve stimulation performed by applying electrode patches to the S2, S3, and S4 dermatomes on the lower back [14]. Participants included 40 women with OAB unresponsive to lifestyle and behavioral therapy. TENS therapy consisted of five sessions per week for a period of two weeks with half of the study population undergoing TENS and the other half undergoing control therapy (application of electrodes but no current applied). The TENS group experienced significant reductions in OAB symptoms with two patients achieving complete continence. Further studies are no doubt

underway and it will be exciting to see what other modalities for at home nerve stimulation will emerge in the coming years.

## Sacral Neuromodulation

Although the efficacy of sacral neuromodulation (SNM) in treated OAB is well established, there have been several notable studies on SNM in the past few years. In 2016, the ROSETTA trial results were published [15••]. The ROSETTA study was a randomized trial of 381 women with refractory UUI (defined as persistent symptoms despite treatment with at least one conservative initial therapy and two antimuscarinic medications) who had at least 6 UUI episodes on a 3-day diary. The investigators compared SNM (two-stage lead placement in the OR) to BoNT/A (cystoscopic intradetrusor injection of 200 units performed in clinic). Overall, more than 80% of participants were clinical responders to their allocated treatment (either SNM or BoNT/A) with an average reduction of three to four UUI episodes per day in both groups. BoNT/A did have a statistically significant greater reduction in daily UUI episodes but the clinical significance is unclear as this was only a mean difference of 0.63 UUI per day (95% confidence interval 0.13–1.14,  $p = 0.01$ ). BoNT/A also had a higher continence rate (20% continence rate with BoNT/A versus 4% with SNM) but carried a higher risk of UTI (35% BoNT/A versus 11% SNM) and a 20% catheterization rate over 6 months of follow-up. Amundsen and colleagues concluded that it is uncertain whether BoNT/A 200 units provides a clinically significant net benefit compared with staged implant SNM, but that both offered effective therapy for UUI.

This year, Siegel and colleagues published 5-year follow-up data from the InSite randomized trial comparing staged implant SNM to standard medical therapy among OAB patients with two or more UUI episodes in a 3-day diary who had failed antimuscarinic medication [16••]. Of the 272 participants implanted, 182 were followed for the 5-year time period. There was a 67% success rate and 38% achieved complete continence at 5 years with an average reduction of two UUI episodes per day. For adverse events, of all 272 initial subjects, the authors reported the following rates of adverse events: 15% implant site pain, 34% battery revision, and 19% permanent explant rate.

Due to the high upfront cost of implantation with SNM, the cost-effectiveness of SNM therapy relies on the long-term efficacy to offset these initial charges. Continued research is needed to determine the long-term outcomes of SNM, such as efficacy, adverse events, and explantation rates. This information is critical to enable accurate cost-analysis assessments. Further studies are also needed to explore predictors of successful response to therapy and elucidate the mechanism of action of SNM therapy.

## Alternative Therapies

For those interested in alternative therapies for OAB, Arnouk and colleagues published a review article this year that examines physical therapy, complementary therapy, and alternative medicine treatments for pelvic floor disorders, including OAB/UUI [17••]. Their manuscript discusses the evidence behind pelvic floor muscle training, behavioral interventions (weight loss, dietary modifications, decreasing straining/constipation, and bladder training), biofeedback, electrical stimulation, acupuncture, and cognitive behavioral interventions. The authors concluded that while the quality of evidence is heterogeneous, all of these treatment options have shown at least a modest benefit for pelvic floor disorders with minimal adverse events.

A recent randomized trial that was not included in Arnouk's review was a study by Yuan and colleagues comparing weekly acupuncture to tolterodine 2 mg twice a day for women with OAB over a 4-week observation period [18]. Participants in both treatment arms had significant decreases in urge episodes, incontinence episodes, frequency, nocturia, and noted increased voided volumes on 3-day diaries. There were no adverse events in the acupuncture group leading authors to conclude that acupuncture is a potentially safe and effective alternative treatment with larger studies needed to further assess efficacy of acupuncture for OAB. Although evidence is limited, alternative treatments, such as acupuncture and cognitive behavioral therapy, have minimal risk and offer an alternative to pharmacologic intervention that will appeal to a subset of the patient population affected by OAB/UUI.

## Emerging Technologies

As neuromodulation and BoNT/A have proven to be such effective therapies for OAB/UUI, investigators are looking for other ways to influence the bladder neuromuscular system that are less invasive but have similar efficacy. One potential modality is magnetotherapy or electromagnetic nerve stimulation, which has been utilized for treatment of urinary incontinence since the 1990s. In 2015, Lim and colleagues published a systematic review examining the efficacy of electromagnetic therapy for urinary incontinence [19]. They included eight studies (two on UUI, one of OAB, two on mixed incontinence, and three on stress incontinence only) with a total of 494 patients. There was considerable variability in frequency and duration of stimulation and the treatment period studied. Magnetic stimulation showed some evidence of improving incontinence symptoms in patients with UUI with no significant differences seen in the one study examining the effect in patients with OAB. The data is sparse and there is enough variability in the specific stimulation protocols that further research is needed before any conclusions can be drawn. Although the clinical utility is not proven at this time,

magnetic stimulation has potential to become a non-invasive therapeutic option for UUI that has minimal adverse effects.

Another experimental treatment that investigators have hypothesized may improve UUI symptoms is vaginal laser therapy. Vaginal laser therapy has recently emerged as a new potential treatment for vaginal atrophy in postmenopausal patients. Perino et al. recently published a study examining the effect of fractional vaginal CO<sub>2</sub> laser in postmenopausal women with vulvovaginal atrophy and OAB [20]. This was a pilot study following 30 participants who received 3 treatments with fractional vaginal CO<sub>2</sub> laser spaced over a period of at least 30 days. The authors found that participants reported an improvement in urge episodes and OAB-q short form score after therapy and no adverse events due to fractional vaginal CO<sub>2</sub> laser. This pilot study has interesting findings but vaginal laser therapy is definitely still experimental, and additional studies, ideally randomized trials, are needed to prove the safety and efficacy of this new potential treatment modality before therapeutic use.

## Looking to the Future

A revolutionary advancement within the field of urogynecology has been the discovery of a urinary microbiome. The term microbiome refers to the genetic material of microorganisms present in a particular environment, in this case the human body. The NIH Common Fund Microbiome Project (the Human Microbiome Project) was established in 2008 to identify and characterize the human microbiome and its role in health and disease. Notably, the bladder was not included as it was widely accepted that urine was sterile. However, in 2011 and 2012, investigators discovered microorganisms in the urine of adult women without clinical evidence of urinary tract infection [21, 22]. The discovery that non-pathogenic bacteria reside in the human bladder has spurred a flurry of investigation into the urinary microbiome and its relation to lower urinary tract function and dysfunction.

As we learn more about the urinary microbiome and the interaction between bacterial species, the host, and the presence or absence of lower urinary tract symptoms, we will no doubt gain new insights into potential treatment options for OAB/UUI. Investigators have already started to characterize the urinary microbiome in women with OAB/UUI compared to women without lower urinary tract dysfunction and are looking to determine if the microbiome can predict treatment response. Preliminary studies have shown that women with UUI have lower *Lactobacillus* and higher *Gardnerella* sequence abundances in their urine [23, 24]. Additional studies have shown that the presence of bacteria in the urine in general and the presence of certain species in the urine of women undergoing therapy for OAB are associated with improved treatment response [25, 26•].

These last two studies bring up an interesting question of whether we would be able to predict response to therapy by the presence or absence of certain microbiota or other urinary biomarkers. Alkis et al. recently published a study examining various urinary biomarkers that have been shown in prior studies to be associated with the presence of OAB and which were shown to actually decrease in response to treatment for OAB [27•]. Alkis and colleagues were looking to see if urinary biomarkers (NGF, GAG, MCP-1, and BDNF) could be used to predict treatment response in patients with OAB prior to initiation of therapy. They examined 90 women (45 with OAB and 45 healthy age-matched controls) treated with solifenacin 5 mg daily for 1 month. The authors found that the level of these biomarkers were higher in the OAB group and did decrease with therapy; however, basal biomarker levels did not significantly differ between women who responded to or who did not respond to antimuscarinic therapy. Although this study failed to discover biomarkers that predict treatment response, it addresses an exciting area of research—will we ever be able to diagnose OAB based on the presence of urinary biomarkers? And will we ever be able to predict who will respond to what therapy? Several studies have attempted to identify characteristics associated with successful treatment response. In fact, in a recent study by Darekar and colleagues, the authors created a model to predict OAB treatment response to antimuscarinic medication [28]. However, as of yet, there is no definitive answer for these questions. A greater understanding of identifiable characteristics of patients who respond to treatment (for example, demographic characteristics, urinary biomarkers, bacteria in the urinary microbiome) will enable us to tailor therapy and set appropriate patient expectations when initiating treatment for OAB/UUI.

As we continue to modify treatment guidelines in the future, it is important to consider the growing evidence to support the effectiveness and improved tolerability of non-pharmacologic interventions (and BoNT/A) as compared to antimuscarinic therapy. Antimuscarinic medications are an effective treatment for OAB, but their efficacy is limited by bothersome side effects with the majority of patients stopping antimuscarinic therapy within 1 year [29, 30]. As seen with the experimental and newer therapies discussed in this review, emphasis is on providing non-invasive therapies that limit patient burden and have low adverse effects. A growing number of studies continue to demonstrate the safety, superior efficacy, and potential cost savings for non-antimuscarinic therapies in the treatment of UUI [3••, 31]. In this era emphasizing patient autonomy and individualized care, people suffering from OAB should be able to choose an intervention that will be safe, tolerable, and effective and one which they will have a high likelihood of continuing to use. They should not be required to undergo therapy with medications that have limited efficacy and significant side effects (including cognitive impairment) before moving to other options. Therapy should be tailored to the individual's risk preferences and lifestyle.

## Conclusion

OAB/UUI is a complicated condition treated by a wide variety of therapies ranging from treatments as simple as decreasing fluid intake to those as complex as direct nerve fiber stimulation. Non-pharmacologic therapies provide an important and necessary component for treating those suffering from UUI. The discovery of neuromodulation therapy and the urinary microbiome is transforming our approach to treating this burdensome condition. As we continue to learn more about OAB/UUI and determine effective treatment options, it will be exciting to see what other non-pharmacologic interventions are discovered.

## Compliance with Ethical Standards

**Conflict of Interest** Alexis A. Dieter declares that she has no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by the author.

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